REMARKS

All the claims submitted for examination in this application have been rejected on substantive grounds. Applicants have amended their claims and respectfully submit that all the claims currently in this application are patentable over the rejection of record.

Two substantive grounds of rejection are imposed in the outstanding Official Action. The first of these is directed to Claims 1, 3, 5 and 7. Claims 1, 3, 5 and 7 stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Collins, *Clin. Cancer Res., 6*:1203-1204 (2000) taken in view of Beulz-Riché et al., *Cancer Chem. Pharm, 49*:274-280 (2002).

The Official Action avers that Collins teaches a method of testing CYP3A and predicting dosage levels. The Official Action admits, however, that Collins does not disclose that this method can be used with nemorubicin. Thus, the Official Action applies Beulz-Riché et al. for its teaching that nemorubicin is metabolized by CYP3A. As such, the Official Action concludes that the combined teaching of Collins and Beulz-Riché et al. provides a method of testing CYP3A to determine the necessary level of nemorubicin required in treatment.

Applicants have considered this ground of rejection and believe that the Official Action interpretation of the teaching of Collins is misplaced. That is, Collins merely teaches that the erythromycin breath test, denoted in Collins as ERMBT, is an excellent test to determine docetaxel metabolism. Indeed, this test can be used to shield patients from the toxic effects of docetaxel when it is found that the CYP3A levels indicate that docetaxel will be too rapidly eliminated from the body.

The secondary Beulz-Riché et al. article discloses the effects of docetaxel, cyclosporine, cyclophosphamide, ifosaimide and tamoxifen on the metabolism of doxorubicin.

When these two teachings are combined, it is apparent that they do not make obvious any of the amended claims currently in this application. The amended claims of the present application are limited to a method of treating a liver cancer or a liver metastases and a method of predicting sensitivity to nemorubicin in a patient suffering liver cancer or liver metastases. These claimed methods are not taught by the combined teaching of the applied references.

As suggested above, the Collins article teaches the ascertaining of CYP3A levels in a patient to eliminate those patients for whom treatment with docetaxel should be avoided insofar as the docetaxel cannot be retained long enough to provide therapeutical efficacy. Thus, those patients would be subjected to the toxic effects of docetaxel without benefiting from its efficacy.

The claims of the present application, on the other hand, teaches the opposite effect. The claimed method of the present application, directed to a liver cancer or a liver metastases patient only, utilizes detection and determination of CYP3A levels to identify those patients who can benefit from a totally different drug, nemorubicin, because CYP3A enzymes generate a metabolite, when nemorubicin is administered, more active than nemorubicin, that has increased efficacy in the treatment of liver cancer and liver metastases.

In other words, whereas Collins teaches that CYP3A enzymes convert docetaxel into metabolites that are then excreted and thus teaches a method of exclusion of cancer patients to treatment with docetaxel, the present invention provides a method of inclusion of liver cancer or liver metastases patients to treatment with nemorubicin.

It is apparent that although docetaxel, discussed in Collins, is, like nemorubicin, metabolized by CYP3A enzymes, the therapeutic effect is different owing to the different properties of the resultant metabolites. As such, not only is there no equivalence between the

teaching of docetaxel, as taught by Collins, with the claimed nemorubicin but that alleged equivalence teaches away from present invention. The teaching of Collins suggests that the detection and determination of CYP3A levels should be used to eliminate treatment with a first cancer drug. The present invention is used to encourage use of a second cancer drug, which acts totally differently than the first cancer drug.

The above arguments have been emphasized by the amended language of the claims. Although the claims had previously been limited to nemorubicin, and thus distinguish significantly from the combined teaching of Collins and Beulz-Riché et al., the present amendment, limiting the claims to patients suffering from liver cancer or liver metastases, emphasize this distinction insofar as it is in the liver where nemorubicin is activated by the formation of an active metabolite that enhances its efficacy in the treatment of liver cancer or liver metastases.

Applicants submit that the amendment to the claims add no new matter to the application. The specification, at Page 6, lines 17-20, emphasizes that nemorubicin is useful in treating a liver cancer or a liver metastases. Furthermore, the added matter in Claim 1, the formation of a metabolite of nemorubicin more active than nemorubicin, is supported by the specification at Page 2, lines 9-15.

Turning now to the second substantive ground of rejection, Claims 11-14 stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Collins taken in view of Beulz-Riché et al.

The Official Action states that Claims 11-14 depend from Claims 1, 3, 5 and 7, respectively. In each case, the method of detecting CYP3A levels is further limited to an erythromycin breath test (ERMBT). Since, the ERMBT is used by Collins to measure CYP3A

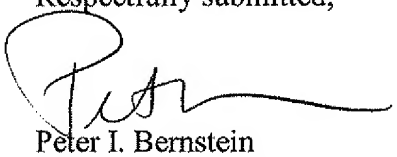
levels, the Official Action argues that it would have been obvious to use that test to optimize the dosages of nemorubicin as taught by Beulz-Riché et al.

Applicants do not allege that the detection or determination of CYP3A levels by the ERMBT is a patentable advance. However, the above remarks, establishing the patentability of Claims 1, 3, 5 and 7, are relied upon in support of the patentability of Claims 11-14, respectively, which depend from Claims 1, 3, 5 and 7. That is, the above remarks, which emphasize the patentability of the methods of Claims 1, 3, 5 and 7, serve to provide the patentable distinction of Claims 11-14 over the same combined prior art teaching applied in the rejection of the independent claims from which these claims depend.

Applicants submit that entrance of the present amendment, after final rejection, is appropriate. It is axiomatic that an amendment which places claims in condition for allowance or at least places them in better condition for appeal should be entered. The amendment to the claims of the present application better emphasize the distinction of the present invention over the teachings of the prior art. As such, this amendment meets the aforementioned requirements for introduction of an amendment after final rejection.

The above amendment and remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and the passage of issue of these claims, Claims 1, 3, 5, 7 and 11-14, is therefore respectfully solicited.

Respectfully submitted,



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